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Maternal Serum Markers Levels in Consecutive Pregnancies: A Possible Genetic Predisposition to Abnormal Levels

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The study comprised 2,361 women, each with two consecutive normal uncomplicated pregnancies screened at 15–20 weeks gestation for maternal serum alpha-fetoprotein levels (AFP). In 1,816 of these women, maternal serum human chorionic gonadotropin (hCG) levels were tested as well. The proportion of women who had a second high AFP level (≥2.0 MOM) in their subsequent pregnancy was 6.5-fold higher as compared with the proportion of women who had normal levels of AFP in their first tested pregnancy. The relative chance of having a second positive result of a low level of AFP (AFP ≤0.5 MOM) in subsequent pregnancies was 3.8-fold higher. The relative chances of having a second positive result of high or low levels of hCG were 3.9- and 2.2-fold higher, respectively. It is concluded that there is a predisposition for abnormal levels of serum markers that is influenced by genetic and/or environmental factors. Therefore it is suggested that the individual's risk of having a Down syndrome baby, or other adverse pregnancy outcome that is derived from the serum markers' levels, should be adjusted taking into account unexplained *high or low levels in previous pregnancies*. A screening policy is suggested which is designed to yield a lower false-positive rate without affecting the detection rate of abnormal pregnancies. More data are needed before an accurate adjustment based on previous results can be made.

KEY WORDS: prenatal diagnosis, screening, AFP, hCG, Down syndrome, NTD

INTRODUCTION

Antenatal screening for neural tube defects and Down syndrome (DS) using maternal serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3) has become a common practice.

Elevated AFP levels have been associated with an increased risk for neural tube defects (NTD) and abdominal wall defects [Milunsky, 1980; Palomaki et al., 1988]. Elevated levels of hCG with low levels of AFP and low levels of uE3 have been associated with an increased risk for DS [MacDonald et al., 1991; Haddow et al., 1992].

Based on the accumulated data, the individual's risk of having a DS pregnancy may be derived [Wald et al., 1988].

In the absence of fetal anomalies, elevated levels of AFP at 15–20 weeks gestation have been correlated with a variety of adverse pregnancy outcomes, including intrauterine fetal death, intrauterine growth retardation, and prematurity [Nelson et al., 1987; Robinson et al., 1989].

Elevated levels of hCG have been associated with preeclampsia, intrauterine growth retardation, and preterm delivery [Gonen et al., 1992; Gravett et al., 1992].

An increasing number of women have been tested in more than one pregnancy. The question was raised whether a woman who had unexplained pathological levels of serum markers in one pregnancy is more likely to have similar results also in her subsequent pregnancy. Such predisposition for positive results might indicate the possible involvement of genetic factors or environmental factors that might predispose for abnormal high or low levels of maternal serum markers.

A higher than expected proportion of two consecutive pregnancies with raised levels of AFP (>2.5 MOM) was reported by Wald and Cuckle [1981]. It was stated that the difference found was probably too small to be of practical importance. In another letter to the editor by Holding and Cuckle [1994] a positive between-

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pregnancy correlation for serum markers AFP, hCG, and uE3 was reported, and data showing an increased likelihood of having positive result using a cutoff of 1:250 risk for DS were presented.

The purpose of this study was to further clarify the possibility that a woman who has shown abnormally high or low levels of serum markers in a previous pregnancy has an increased likelihood of having similar results in her subsequent pregnancies. Such a positive correlation should be taken into account when risk estimations for DS, NTD, or other adverse pregnancy outcomes, based on serum markers levels, are calculated.

SUBJECTS AND METHODS

The study comprised 2,361 women, each with 2 consecutive unaffected and uncomplicated singleton pregnancies, enrolled in the prenatal screening program conducted in Bnai-Zion Medical Center between 1988 and 1994. The women were screened at 15–20 weeks gestation for AFP levels. In 1,816 of the women, hCG levels were tested as well. Cases with fetal anomalies, chromosome aberrations, or diagnosed pregnancy complications such as stillbirth, twins, threatening abortion, oligo- or polyhydramnios, placental abnormalities, and preeclampsia were excluded from the study. All relevant data concerning pregnancy complications and pregnancy outcomes were obtained from hospital delivery records.

Our patients' population was composed mainly of middle-class women, 60% of whom were Jewish and 40% were either Arab or Druze.

Serum AFP and hCG levels were measured using Delfia kits (Pharmacia, Turku, Finland). The markers' levels were expressed in multiples of medians (MOM), and the results were adjusted for maternal weight. Gestational age was determined by last menstrual period or by ultrasound when available. Ultrasound examinations were requested in all cases with high or low levels of AFP and/or hCG, and gestational age was corrected if indicated.

RESULTS

The median values in MOMs for hCG and for AFP in each of the ethnic groups studied, Jews, Arabs and Druze, were not significantly different. Therefore no further stratification by ethnic background was done. Between-pregnancies correlation coefficients calculated for AFP and hCG levels were r = 0.328 and r = 0.304, respectively. All were statistically significant ($P < 0.001$).

The women were divided into subgroups according to the serum markers' levels. Levels of ≥2.0 MOM were defined as high levels. Levels of ≤0.5 MOM were defined as low levels.

Table I shows the levels of maternal serum markers AFP and hCG in two consecutive pregnancies. A total of 21.6% (16/74) of women who had a high level of AFP in their previous pregnancy had a high level of AFP in their subsequent pregnancy as well, compared to only 3.3% (76/2,287) of women with a normal AFP level in their previous pregnancy who had a raised level in the subsequent pregnancy. The difference is highly significant ($\chi^2 = 64.09$, $P < 0.001$).

The proportion of women who had a second high AFP level (positive result) in subsequent pregnancies (Table I, c/b), was 6.5-fold higher as compared to the proportion of women who had positive results only in their second pregnancy (b). Similarly, the proportion of women who had a low level of AFP in their subsequent pregnancy was 3.8-fold higher in women who had a low level of AFP also in their previous pregnancy. The relative changes for positive results of high or low hCG levels in subsequent pregnancies were 3.9 and 2.2 times higher, respectively. All differences are highly significant ($P < 0.001$).

Figure 1a shows the medians of AFP levels in two consecutive pregnancies in 74 women with high levels of AFP in their first tested pregnancy. The median AFP level in their subsequent pregnancy (1.36 MOM), is significantly higher as compared to that of the general population ($P < 0.001$).

Forty out of 58 women (69%) with high AFP in their first pregnancy showed AFP levels >1.0 M in their subsequent pregnancy.

Figure 1b shows the medians of AFP levels in two consecutive pregnancies in 70 women with low levels of AFP in their first tested pregnancy. The median AFP level in their subsequent pregnancy (0.76 MOM), is significantly lower as compared to that of the general population ($P < 0.001$).

Figure 2 shows the respective medians of hCG levels in 2 consecutive pregnancies in 206 women with high levels of hCG in the first tested pregnancy (Fig. 2a) and

TABLE I. Maternal Serum Markers in Two Consecutive Pregnancies and the Relative Risks for a Second Positive Result

		Positive only in one pregnancy		Positive in 2 pregnancies (c)	Relative risk for a second positive result (c/b)
		First (a)	Second (b)		
AFP	≥2.0	58/2,269	76/2,287	16/74	6.5*
n = 2,361		(2.6)	(3.3)	(21.6)	
	≤0.5	63/2,294	60/2,291	7/70	3.8*
		(2.7)	(2.6)	(10.0)	
hCG	≥2.0	161/1,681	90/1,610	45/206	3.9*
n = 1,816		(9.6)	(5.6)	(21.8)	
	≤0.5	137/1,558	206/1,627	52/189	2.2*
		(8.8)	(12.7)	(27.5)	

*The risk for a second positive result is significantly increased ($P < 0.001$).

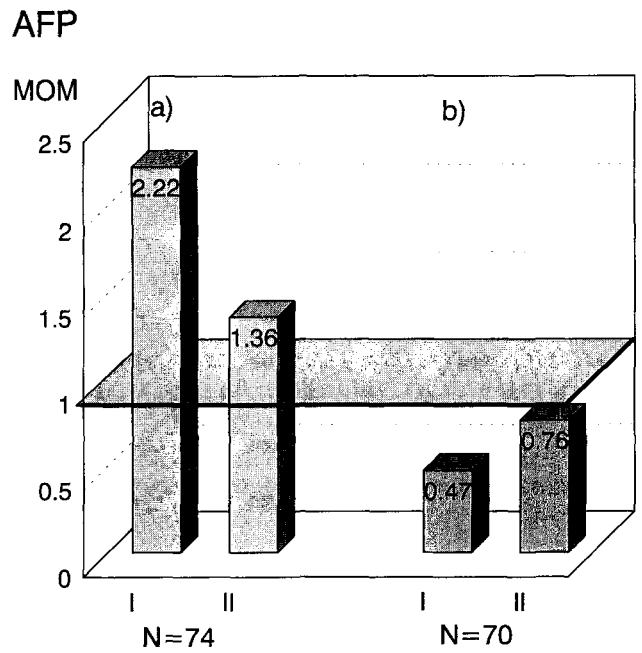

Fig. 1. Median levels of AFP in two consecutive pregnancies given a positive result in the first pregnancy. **a:** AFP ≥ 2.0 MOM. **b:** AFP ≤ 0.5 MOM.

in 189 women with a low level of hCG in their first pregnancy (Fig. 2b). All the differences as compared to the general population are highly significant ($P < 0.001$).

DISCUSSION

The efficiency of antenatal serum markers screening for NTD and for DS is well established [Milunsky, 1980; Haddow et al., 1992], yet the factors involved in causing abnormal high or low serum markers' levels are not fully understood. Fetal anomalies and diagnosed pregnancy complications account for only a small percentage of the abnormal serum markers' levels, while most cases with abnormal serum markers' levels remain unexplained (i.e., false positive).

Racial variations in maternal serum markers' levels have been reported [Baumgarten, 1986]. These variations might be caused by different genetic and/or environmental factors.

Our results confirm the between-pregnancy consistency in AFP and in hCG levels in subsequent pregnancies [Wald and Cuckle, 1981; Holding and Cuckle, 1994]. This consistency further emphasizes the possibility that genetic and/or environmental factors play a role in serum markers' levels determination.

On the basis of the present data, a woman with an unexplained high AFP level (≥2.0 MOM) in a previous pregnancy, has an increased chance of a second positive result, which is about 7 times the general chance of having a high level. The chance for a woman with an unexplained low AFP level (≤0.5 MOM) in a previous pregnancy of having a positive result in the next pregnancy is approximately 4-fold greater. The same trend is presented for the high and the low levels of hCG (Table I).

Based on the data in Figures 1 and 2, a screening policy is suggested which is designed to yield a lower false-positive rate without affecting the detection rate of abnormal pregnancies. This may be achieved by adjusting the values in the consecutive pregnancy of a woman who had a previous positive result. The suggested correction factor is the median of the respective serum marker in the group of consecutive pregnancies, as shown in Figures 1 and 2. Thus, the AFP levels of women with unexplained high AFP levels in first pregnancy, should be divided by a correction factor of 1.36, and the AFP levels of women with unexplained low AFP levels in first pregnancy, should be divided by a correction factor of 0.76 (Fig. 1). The correction factors for unexplained positive results of hCG are 1.37 and 0.68, respectively (Fig. 2). Using these data, the calculated estimated risks for DS or for other adverse pregnancy outcomes, can be adjusted, taking into account unexplained positive results in previous pregnancies.

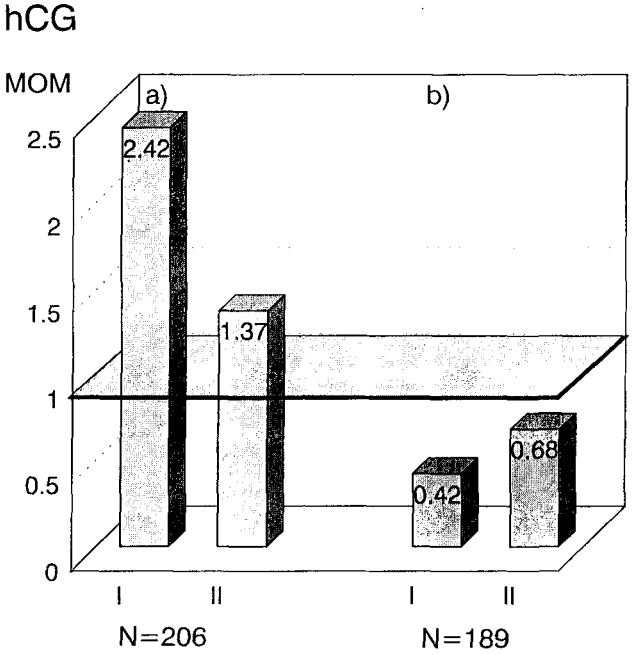

Fig. 2. Median levels of hCG in two consecutive pregnancies given a positive result in the first pregnancy. **a:** hCG ≥ 2.0 MOM. **b:** hCG ≤ 0.5 MOM.

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